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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,364	05/25/2001	Saburo Sone	04853.0071	1599

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/864,364	SONE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-18 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-18 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/11/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response and amendment filed 8/11/04 have been entered. Claims 1, 10, 13-16 have been amended, and claim 19 has been canceled. Currently, claims 1-5, 7, 9-18, and 21-25 are pending and under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and argument will not be reiterated. The arguments in 8/11/04 response would be addressed to the extent that they apply to current rejection.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Applicants requested indication of specific deficiency, which is now being underlined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9-18, 21-25 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a rodent bone metastasis model animal by intravenous administration of human lung small cell carcinoma cell line SBC-5 cells, wherein the rodent is immunodeficient, does not reasonably provide enablement for producing a rodent bone metastasis model animal by intravenous administration of *any* human cancer or tumor cells that highly express PTHrP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect to the type of tumor cells, applicants argue that the citations do not bear the weight the Examiner gives it, the enablement is not disproved simply because there are alternative ways of reaching a similar results.

In response, as an initial matter, it is noted applicants indicated in 8/11/04 response that "and highly express PTHrP" means "PTHrP can be detected in the concentration higher than that detected in normal individuals" (page 12 of the response). The references were cited because the claims recite "tumor cells that induce bone metastasis and highly express PTHrP". The referred citations are

intended to show it is unpredictable concerning which type of tumor cells that (1) highly express PTHrP and (2) also induce bone metastasis, because just knowing a type of tumor cells that express PTHrP highly, does not necessarily indicate that these cells would induce bone metastasis. For example, all of the four tumor cell lines used by Lelekakis et al express higher than normal levels of PTHrP, yet only 4T1 induces bone metastasis via i.v. injection. Lelekakis et al concluded, "the PRESENCE OF PTHRP IN THE TUMOR ALONE IS INSUFFICIENT TO DIRECT SPREAD AND GROWTH SPECIFICALLY IN BONE" (e.g. 4th paragraph, page 169). The specification only discloses one type of tumor cells (SBC-5) having such property (i.e. induce bone metastasis via i.v. injection and highly express PTHrP), which is not a representative species of the genus of tumor cells having such property. It is noted that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Goodman, 29 USPQ2d 2010 (CA FC 1993); In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), the court gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN

APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT." Thus, in light of the teaching of the specification coupled with the state of the art, the specification fails to provide an enabling disclosure to support the full scope of the claims.

Accordingly, for reasons of record and those set forth foregoing, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph commensurate with the scope of claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5, 7, 10, 11, 21, 24, and 25 stand rejected, and the rejection has been modified under 35 U.S.C. 103(a) as being unpatentable over *Lelekakis et al* (Clin Exp Metastasis 1999 Mar;17:163-70), in view of *Seon et al* (US 5,928,641).

In the 8/11/04 response, Applicants argue that the claims amended to using human tumor cells to induce bone metastasis, whereas *Lelekakis et al* use mouse tumor cells.

The arguments have been fully considered but found not persuasive because *Lelekakis et al* teach a mouse model for *human* bone metastasis, wherein they

describe the findings as "THE MODEL IS UNIQUE IN THAT THE PATTERN OF METASTASIS SPREAD CLOSELY RESEMBLES THAT OBSERVED IN HUMAN BREAST CANCER" (2nd paragraph, page 164). *Lelekakis et al* use mouse cells because the model is an immune competent mouse, delivering human cells would cause xenograft rejection in such mouse. However, *Lelekakis et al* do disclose the routine practice of establishing human tumor metastasis model as using an immunodeficient mouse, and *Lelekakis et al* do teach which immunodeficient model has provided strong evidence for the importance of PTHrP in bone metastasis (e.g. last paragraph page 163). However, *Lelekakis et al* do not actually use an immunodeficient mouse having human tumor cells.

Seon et al supplemented the teaching of *Lelekakis et al* by establishing that it is well known in the art at the time of instant filing date, one can use immunodeficient mouse for establish human tumor model, wherein nude or scid mice with human tumor xenografts have been validated as a model for evaluation and studying chemotherapeutic agents (e.g. column 3, § 5).

With respect to selecting tumor cells according to PTHrP expression, *Lelekakis et al* tested four lines of tumor cells, all express PTHrP at higher than normal levels, but only 4T1.2 cells developed bone matestasis. *Lelekakis et al* thus teach, PTHrP is not the only factor for bone metastasis, "NEVERTHELESS, LEVELS OF PTHRP SECREDED BY THE 4T1.2 CELL IN VITRO WERE HIGHER THAN THOSE SECRETED BY THE 66C14 OR 67NR. THUS, IT WOULD SEEM THAT THE HIGHER LEVEL OF CELLULAR PTHRP SECRETION IN VITRO MAY BE ASSOCIATED WITH THE ABILITY TO GENERATE BONE METASTASES IN VIVO" (4th paragraph, page 169).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use an immunodeficient model mouse when studying bone metastasis of human tumor cells and selecting for tumor cells with higher level of PTHrP expression *in vitro* for inducing bone metastasis *in vivo* with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

This conclusion is reasonable particularly in view of applicant's arguments presented in page 11 of the 8/11/04 response, that it is generally known in the art there is a clear correlation between expression of PTHrP and bone metastasis.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306.**

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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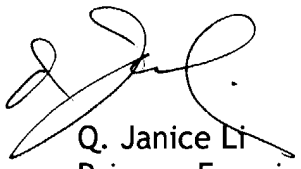

Q. Janice Li
Primary Examiner
Art Unit 1632

QJL
October 26, 2004